REMARKS

Claims 1-6, 8-16, 18-25, 27, 28, 33 and 36-39 are pending in this application. Claims 1-6, 8-16, 18-25, 27, 28, 33 and 36-39 were variously rejected under 35 U.S.C. § 112, first paragraph.

By this amendment, claims 33 and 36-39 have been canceled and claims 1, 10, and 20 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification, for example, at page 17, line 23, and at page 21, line 14. Support for the amendment to claim 1 is found, *inter alia*, at page 35, lines 6-7.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicant has carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Examiner Interview

Applicant and Applicant's representatives thank Examiners Sullivan, Falk and Caputa for an interview on June 16, 2004 regarding the outstanding rejections in this application. Applicant appreciates the Examiners' time and attention, as well as thoughts and suggestions regarding the matter at hand. Applicant acknowledges receipt from the Examiners of U.S. Pat. Application Publication No. 2004-0030118, submitted herewith in a supplemental Information Disclosure

Statement. Applicant received an Interview Summary (PTOL-413) from Examiner Sullivan on June 16, 2004. The topics discussed in the interview and the interview summary are reflected herein.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-6, 8-16, 18-25, 27, 28, 33 and 36-39 were variously rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant respectfully traverses this rejection.

As discussed during the interview, immunostimulatory activity for a particular polynucleotide sequence can, but need not, vary from animal species to animal species. For reasons already of record, Applicant maintains that the specification is enabled for the methods of the invention applied to any mammalian species. However, in order to expedite prosecution, the pending claims have been amended to recite administration of the claimed composition to a single species, human. Accordingly, the presently claimed invention is directed to methods wherein the composition is administered to a human.

The amended claims are directed to methods of preventing a symptom, reducing severity, and reducing recurrence of a symptom of herpes simplex virus infection in a human comprising administering an ISS-containing polynucleotide composition in the absence of administration of a herpes simplex virus antigen. In the claims, the ISS comprises the sequence 5'-C, G-3' and the polynucleotide is greater than 6 nucleotides and less than about 200 nucleotides in length and comprises a phosphate backbone modification.

The Examiner's concerns essentially relate to the effective "scope" of enablement, and whether the description and exemplary embodiments adequately support the invention as claimed to

one of skill in the art. In particular, the Examiner states that the disclosure does not "set forth teachings regarding the requirements for an immunostimulatory oligonucleotide effective in humans beyond the sequence set forth as SEQ ID NO:1." Office Action, page 9. Applicant respectfully disagrees with the assertion that the claimed methods are enabled only for a composition comprising SEQ ID NO:1.

As an initial matter, in support of the rejection under a heading of "Nature of the invention and Breadth of the claims," the Examiner states that "[a]s the claims are not limited to any particular ISS, the claims broadly encompass treating a human with any nucleic acid comprising the dinucleotide 5'-C, G-3'." Office Action pages 6-7, emphasis added. Applicants respectfully point out that, in addition to including a CG dinucleotide, the polynucleotide administered in the claimed invention is greater than 6 nucleotides and less than about 200 nucleotides in length and comprises a phosphate backbone modification. Thus, the claims are not as broad as characterized by the Examiner.

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); M.P.E.P. §2164.04. In support of the rejection, the Examiner points to the Agrawal and Hartmann references[1] as demonstrating "the unpredictability of obtaining a useful response to any given CpG-containing oligonucleotide in any given species." Office Action, page 8. Applicant respectfully submits that these references demonstrate variance in the level of immunostimulatory activity among particular polynucleotides and the optimization of polynucleotide sequences for immunostimulatory activity, particularly activity in human cells.

[1] Agrawal et al. (2002, *Trends in Molecular Medicine* 8:114-121; "Agrawal") and Hartmann et al. (2000, *J. Immunol.* 164:1617-1624; "Hartmann"), both of record.

These references, however, do not support a state of the art such that the claimed invention is not enabled.

As discussed during the interview, Agrawal is focused on optimizing CpG sequences for immunostimulatory activity and "optimal design of second-generation CpG DNA." Agrawal, page 119. The focus on optimization in Agrawal is also reflected in the statements from the reference quoted by the Examiner on pages 7-8 of the Office Action. Agrawal describes that the CG dinucleotide is essential for the induction of immunostimulatory activity and that one can optimize the immunostimulatory activity of the polynucleotide for a particular animal species by changing flanking sequences. That the activity of a polynucleotide may be fine-tuned by sequence adjustments does not indicate a lack of enablement for the instant specification. Agrawal does not support the need for undue experimentation for the claimed invention.

Hartmann also discusses sequences containing a CG dinucleotide that are optimized for immunostimulatory activity. Some of these oligonucleotides have immunostimulatory activity across animal species and some appear to vary in activity level depending on the recipient animal species.

For example, Fig. 2 of Hartmann depicts results for the screening for the optimal sequences of oligonucleotide to activate human NK and B cells. The tested oligonucleotides were greater than 6 and less than 200 nucleotides in length and had a phosphate backbone modification. As shown in Fig. 2, 75% (15/20) of the CG containing oligonucleotides were active in stimulating both types of human cells. Table II of Hartmann presents results where 80% (4/5) CG containing oligonucleotides stimulated human peripheral blood mononuclear cells (PBMCs). Of the four CG containing oligonucleotides immunostimulatory for human cells, two of the oligonucleotides were immunostimulatory for chimpanzee PBMCs and for rhesus monkey PBMCs as well. Experimental

results in Hartmann indicate that the level of immunostimulatory of some oligonucleotides can vary depending on the recipient animal species. However, taken in its entirety, Hartmann does not support the need for undue experimentation for the claimed invention. Indeed, the court found in *in re Wands* the enablement requirement met even though 4 of 9 antibodies analyzed (44%) were found to have the claimed binding requirements and those successful 4 were produced in only 2 of 10 fusion experiments. *In re Wands*, 858 F2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Hartmann, in fact, teaches many CG containing oligonucleotides that are immunostimulatory for human cells and describes methods to identify and test sequences optimized for activity in humans. Accordingly, Hartmann demonstrates that immunostimulatory polynucleotides sequences active in human cells as well as methods to identify and test for such sequences were known in the art at the time the instant application was filed.

The Examiner states that "Hartmann et al. also teach that the effectiveness of any given ISS is unpredictable even within closely related mammalian species" and quotes from Hartmann that "[a]lthough ODN 2006 was active in vitro in all primates tested, other CpG ODN, such as ODN 2007, had relatively high activity in human immune cells but no or a weaker effect in chimpanzees and rhesus monkeys." The Examiner then concludes that "[t]hese teachings demonstrate the unpredictability of obtaining a useful response to any given CpG-containing oligonucleotides in any given species." Office Action, page 8, emphasis added.

As agreed on during the interview, fulfillment of the enablement requirement does not require that every embodiment of the invention be predictable. Rather, unpredictability is permitted, the level of unpredictability permitted depending on the level of guidance provided by the specification and the knowledge in the art. Applicant respectfully notes that the test for enablement is not whether a certain amount of experimentation is required to practice an invention,

but rather whether the amount of experimentation is "undue." *In re Wands*, *Supra*, (Fed. Cir. 1988). Applicant respectfully submits that the specification has provided a reasonable amount of guidance to the skilled artisan with respect to the identification and testing of polynucleotide sequences with immunostimulatory activity in humans and that the skilled artisan would be able to extend the teachings of the specification and the art to other immunostimulatory polynucleotides as claimed.

The Examiner cites Pyles *et al.* as supporting SEQ ID NO:1 as capable of eliciting an effective immune response in humans and thus enabled for the claimed methods directed to humans. Applicants note that the citation in Pyles *et al.* pointed out by the Examiner indicates that an oligonucleotide with this sequence was shown to have immunostimulatory activity in human clinical trials. It appears as though the Examiner is asking that a particular immunostimulatory sequence demonstrate activity in a human clinical trial in order to fulfill the enablement requirement for the claimed methods. Certainly, this is not a proper standard for enablement of this invention. The court has stated in both the pharmaceutical and medical device fields that "Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings" and that FDA approval "is not a prerequisite for finding a compound useful within the meaning of the patent laws." *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995); *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

The court in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. "Since one embodiment is ... disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art

without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d. 788, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Applicant respectfully submits that the specification provides a reasonable amount of guidance to the skilled artisan with respect to the direction in which the experimentation should proceed to optimize the teachings of the specification and the art and that any additional necessary experimentation is presumed to be within the level of ordinary skill in the art.

The specification provides adequate guidance to enable one skilled in the art to make and use the claimed invention. Many examples of CG containing immunostimulatory polynucleotides for use in the invention and methods for their synthesis are provided, for example, on pages 24-34. Examples of administration regimens are provided, for example, on pages 34-35. Examples of formulations are provided, for example, on pages 35-36. Examples of dosage ranges of immunostimulatory, CG containing polynucleotides for use in the claimed methods are provided, for example, on page 36. Examples of means of administration are provided, for example, on pages 37-38. Means of assessing the functional activity of the immunostimulatory, CG containing polynucleotides as claimed are provided, for example, on pages 38-40. The working examples in the specification (pages 42-48) exemplify immunostimulatory, CG-containing polynucleotides with activity as claimed. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

According to the Office, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. §112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider obvious. M.P.E.P. §2164.08. The court has stated that "Enablement is not precluded by the necessity for some experimentation such as routine screening ...". *In re Wands*, 858 F2d 731, 8 USPQ2d 1400

(Fed. Cir. 1988). Applicant respectfully submits that varying the nucleic acid sequence of oligonucleotides and testing the oligonucleotides for immunostimulatory activity are well within the bounds of routine experimentation by one of skill in the art.

Thus, Applicant respectfully submits that a *prima facie* case of lack of enablement has not been established.

With regard to the claims directed to a method of preventing a symptom of herpes virus, the Examiner states that "the specification must teach the skilled artisan how to treat a human who has been exposed to herpes simplex virus such that a symptom of herpes simplex virus infection does not appear." Office Action, page 7, emphasis added. As described in the specification, for example, at pages 38-39, and known in the art, herpes simplex infection has a number of symptoms, including but not limited to asymptomatic viral shedding. Accordingly, Applicants respectfully submit that these claims are enabled.

The Examiner also asserted that "to be effective in preventing a symptom the immunostimulatory sequence would have to be administered within a narrow window of time after infection." Office Action, page 9. In an effort to expedite prosecution, such claims have herein been amended to recite that administration occurs prior to 3 days after exposure.

As discussed in during the interview, additional support for the instant invention can be found in several post-filing publications,[2] submitted herewith in a supplemental Information Disclosure Statement.

[2] Harandi et al., 2003, *J. Virol.* 77:953-962; Ashkar et al., 2003, *J. Virol.* 77:8948-8956; Herbst et al., 2003, *J. Antimicrobial Chemotherapy* 52:887-889.

As outlined herein, a *prima facie* case of lack of enablement has not been established and the specification provides considerable guidance as to how to identify and make immunostimulatory, CG containing polynucleotides for use in the invention and how to assess the activity of CG containing polynucleotides in the claimed methods. Thus, Applicant submits that, following the reasoning in the *In re Wands* decision, the disclosure is adequate to enable the invention as claimed.

Accordingly, the pending claims are in compliance with the enablement requirements.

Thus, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001100.

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